



A Population-Based Study of Pediatric and Adult Brainstem Glioma: Prognostic Nomograms for Overall and Cancer-Specific Survival

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ABSTRACT

AIM: To establish an effective predictive model to inform clinical practice for brainstem glioma, a rare and highly aggressive tumor of the central nervous system, given the lack of prior retrospective studies using the SEER database that have included both pediatric and adult patients.

MATERIAL and METHODS: Cases of brainstem tumors diagnosed between 2000 and 2022 were identified from the SEER database. X-tile software and Maxstat were used to define the optimal tumor size cutoff value and risk subgroups for brainstem glioma. Independent prognostic factors were determined using univariate and multivariate Cox proportional hazards regression. These factors were used to construct two nomograms predicting 1-, 2-, and 3-year overall survival and cancer-specific survival for brainstem glioma.

RESULTS: Age, tumor size, histological type, surgery, radiation, and chemotherapy were identified as independent prognostic factors for overall and cancer-specific survival. Notably, gross total resection was significantly associated with improved survival outcomes.

CONCLUSION: This work enhances our understanding of the prognosis of brainstem glioma and corroborates the importance of surgical resection as a prognostic factor in its management. The validated nomograms offer a superior and personalized tool for risk stratification and prognostic estimation, which may be helpful for clinical decision making and patient counseling.

KEYWORDS: Brainstem glioma, SEER database, Nomogram, Prognosis

ABBREVIATIONS: BG: Brainstem glioma, OS: Overall survival, CSS: Cancer-specific survival, AUC: The area under the curve, DCA: Decision curve analysis, K-M: Kaplan-Meier, ROC: Receiver operating characteristic, DSW: Divorced & Separated & Widowed, GTR: Total gross resection, DIPG: Pediatric diffuse pontine intrinsic gliomas

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INTRODUCTION

Brainstem tumor is a specific subgroup of primary brain tumors, with origins in the midbrain, pons, or medulla oblongata. Of these, brainstem glioma (BG) is the most common (2,27). According to the latest report of the Central Brain Tumor Registry of the United States (CBTRUS), 3.8% of all gliomas originate in the brainstem (32). BGs are a heterogeneous group of neoplasms with different ages at onset, clinical and radiological appearance, biological behavior, and disease course (35). These cancers can occur at any age but are mostly diagnosed in younger patients (2,27), accounting for 10%–20% of all pediatric brain tumors (38). BG incidence in adults is much lower (11). The heterogeneity of BG accounts for a broad spectrum of survival outcomes, with a median overall survival (mOS) of 30–40 months, and 5-year survival rates between 45% and 58% (11,13,17,39).

BG is a rare and highly aggressive malignancy of the central nervous system. The brainstem's critical involvement in regulating vital functions imposes significant constraints on therapeutic interventions. Surgical resection, radiotherapy, and chemotherapy are associated with elevated morbidity risks and frequently exhibit suboptimal treatment efficacy (16). Meanwhile, brainstem tumors frequently compress or infiltrate adjacent critical regions, further contributing to the poor prognosis characterized by limited survival and complex clinical management (44).

In the field of oncology, nomograms have become a prevalent graphical tool for prognostic prediction (1,25,43), becoming a standard instrument for various malignancies (4,21). To date, no retrospective studies based on the Surveillance, Epidemiology, and End Results (SEER) database have included both pediatric and adult BG patients. The objective of this study is to identify prognostic factors influencing overall survival (OS) and cancer-specific survival (CSS) in BG. In addition, the study aims to develop validated nomograms for predicting 1-, 2-, and 3-year OS and CSS probabilities.

MATERIAL and METHODS

Data Source

The data were obtained from the SEER database, which is maintained by the National Cancer Institute and covers approximately 30% of the U.S. population. SEER*Stat software, version 8.4.5 (<http://www.seer.cancer.gov/seerstat>), was used to identify patients from the SEER 17 Registries Research Database (November 2024 submission, encompassing the years 2000–2022). Patients from these groups with a primary tumor site (C71.7) in the brainstem were identified. Case identification produced a total of 5,034 cases from these groups in the starting set.

Demographic variables were collected, including age at diagnosis, sex, race, and marital status. Tumor- and treatment-related variables were Collaborative Stage (CS) tumor size, surgical procedure at the primary site (RX Sum—Surg Prim Site, 1998+), histologic type based on ICD-O-3, administration of

radiation therapy, chemotherapy, survival months, vital status, and cause-specific death classification.

Ethical Statement

The present study was conducted with data obtained from the SEER database, which anonymizes and de-identifies all patient information. Consequently, the study was conducted in accordance with the 1964 Helsinki Declaration, and was deemed exempt from the requirement of ethical approval.

Cohort Selection

The inclusion criteria were defined by the following ICD-O-3 histology codes: 9440, 9441, 9442, 9381, 9384, 9400, 9401, 9410, 9411, 9420, 9421, 9424, 9382, 9450, 9451, 9460, 9391, 9392, 9393, and 9380 (26).

The exclusion criteria were CS tumor size values identified as having potential for missing data (989, 888, and unknown); “unknown” documented for the race or survival months of the subject; marital status of “unknown,” “unmarried,” or “domestic partner”; and an RX Sum—Surg Prim Site (1998+) variable of code 99, representing unknown information. Finally, given the anatomical constraints of the brainstem, cases with recorded tumor sizes exceeding 180 millimeters were excluded from the study (Figure 1A).

Statistical Analysis

All statistical analyses were performed using R software (version 4.5.1). All variables were treated as categorical and compared using either Chi-squared or Fisher's exact tests, as appropriate. X-tile software was used to conduct a best cutoff value for tumor size (Figure 1B). The entire cohort (n=1660) was randomly partitioned into a training set (n=1162) and a testing set (n=498), at a ratio of 7:3. The primary endpoints were OS and CSS, which reflect distinct clinical outcomes.

Univariate and multivariate Cox proportional hazard analyses were performed, and independent prognostic factors for BG were identified. From these results, we developed two nomograms to calculate one-, two-, and three-year-OS and CSS rates. The nomograms are accessible via an online calculator located at: <https://pmdb.shinyapps.io/brainstem-glioma-predictor/>. To evaluate the predictive ability of the nomograms, we applied various approaches, including receiver operating characteristic (ROC) and area under the receiver operating characteristic (AUC) curves, concordance index (C-index), calibration curves, and decision curve analysis (DCA) to evaluate discriminative performance and net benefit.

We used the “maxstat” method to identify an optimal risk score cutoff to categorize patients into high and low-risk groups, and then compared their survival outcomes with Kaplan–Meier curves. Meanwhile, survival probabilities of patients treated with gross total resection (GTR), radiation, and chemotherapies combined were estimated. P-values<0.05 were considered statistically significant for all analyses except the univariate Cox regression, for which a criterion of P<0.10 was employed for inclusion in the models.

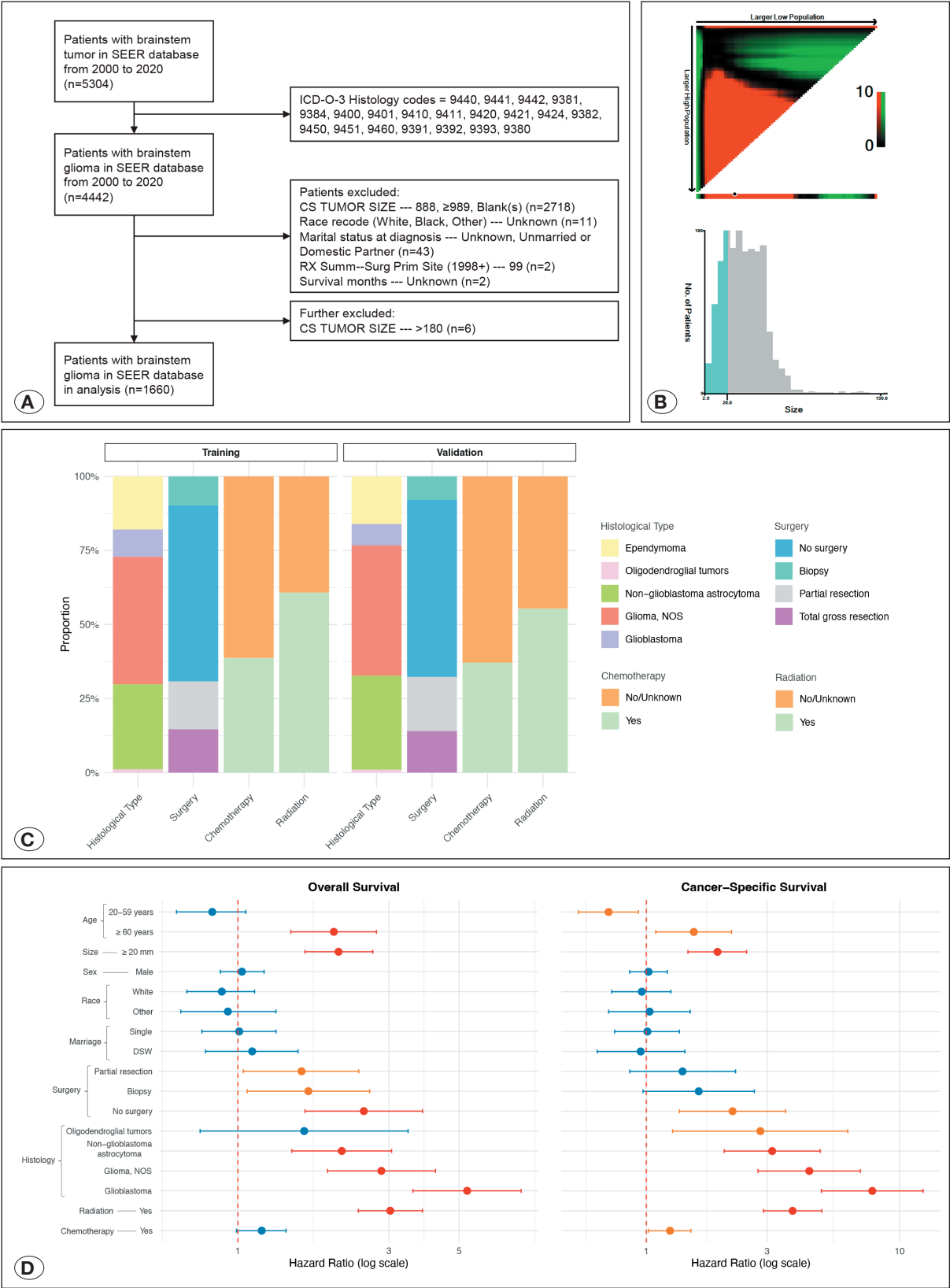


Figure 1: Flow chart of patient selection (A). The best CS tumor size cut-off value by X-tile (B). Distribution of tumor, and treatment characteristics of brainstem glioma patient from the SEER (C). Univariate Cox regression analysis of factors associated with overall survival and cancer-specific survival of brainstem glioma (D).

■ RESULTS

Patient characteristics

After careful inclusion and exclusion procedures, we identified 1,660 patients diagnosed with BG who were considered for the final analysis. Patients were randomly split into a training set ($n=1162$, 70%) and a testing set ($n=498$, 30%). With respect to the dimensions of the neoplasms, 79% of the patients ($n=1313$) exhibited lesions measuring ≥ 20 mm. The most prevalent histological subtypes were glioma, NOS (43%, $n=719$); non-glioblastoma astrocytoma (30%, $n=492$); ependymoma (17%, $n=288$); glioblastoma (8.6%, $n=143$); and oligodendroglial tumor (1.1%, $n=18$). With respect to treatment modalities, the majority of patients (60%, $n=988$) did not undergo surgical resection, with GTR performed in 14% ($n=240$). Partial resection and biopsy were conducted in 17% ($n=279$) and 9.2% ($n=153$) of cases, respectively. Overall, 59% of patients ($n=982$) received radiation therapy, while 62% ($n=1025$) did not receive chemotherapy (Figure 1C). More details about patient characteristic shows in Table I.

Risk Factors for Brainstem Glioma

Nine factors were incorporated into a univariate Cox proportional hazards regression analysis (Figure 1D). Variables with a significance level of $P < 0.10$ were considered associated with patient prognostic survival and were included in a subsequent multivariate Cox proportional hazards regression model to identify independent prognostic factors.

For both OS and CSS, age 20–59 years was positively associated with BG survival outcome. Age ≥ 60 years, Tumor size ≥ 20 mm, partial resection, biopsy, no surgery, non-glioblastoma astrocytoma, glioma, NOS, glioblastoma, radiation therapy, and chemotherapy were all negatively associated with BG survival outcome (Figure 2).

Performance and Validation of the Nomograms

Based on the independent prognostic factors identified in the training set, prognostic nomograms were developed to predict OS and CSS in patients with BG (Figure 3). These nomograms were also converted into an interactive web-based calculator, accessible at: <https://pmdb.shinyapps.io/brainstem-glioma-predictor/>.

ROC curves, AUC values (Figure 4), and calibration curves (Figure 5 A–D) of OS and CSS exhibited superior discriminative performance compared to any single prognostic factor. DCA (Figure 5E–H) further indicated that the nomograms provided significant net benefits across a range of threshold probabilities, and showed robust predictive utility for survival probability for both OS and CSS.

Finally, the optimal risk score cutoff was determined using the “maxstat” method based on CSS, stratifying BG patients into low- and high-risk groups (Figure 6A,B). Kaplan–Meier survival analysis confirmed that patients in the low-risk group had significantly better prognosis than those in the high-risk group (Figure 6C,D).

Kaplan–Meier Survival Analysis

Based on Kaplan–Meier survival analysis, patients under 60 years of age (Figure 7A) and those with tumor size < 20 mm (Figure 7B) exhibited significantly better OS compared to other groups. With respect to histological type (Figure 7C), the glioblastoma subgroup demonstrated markedly worse OS relative to all other subtypes. Interestingly, neither radiation nor chemotherapy alone was associated with improved OS (Figure 7D,E). Similarly, among combined treatment approaches, patients who received both radiation and chemotherapy showed inferior OS compared to other treatment combinations (Figure 8A). In contrast, GTR was correlated with significantly superior OS, both when compared to other surgical interventions (Figure 7F) and in combination with either radiation or chemotherapy (Figure 8B–D).

■ DISCUSSION

BGs demonstrate significant heterogeneity between pediatric and adult patients, with low incidence but poor prognosis (35). The majority of prior clinical studies on BGs have been limited in scope, consisting primarily of small retrospective cohorts (13,24,45), with the majority concentrating on pediatric diffuse intrinsic pontine glioma. Little literature is available on pediatric brainstem low-grade gliomas and adult BGs. Even when large databases have been included, these studies have largely been conducted independently on either pediatric or adult populations (28,46); this has precluded direct comparisons involving a range of ages and histological subtypes. In this study, we therefore used the very large sample available in the SEER database to analyze clinical cases of BG, aiming to fill the research gap of large sample data with full age and subtype ranges.

Nevertheless, several limitations of this report must be mentioned. Firstly, a retrospective review of the SEER database included findings without uniform information on vital details such as the surgical, chemotherapy, or radiotherapy approaches employed. In addition, the database did not include representation from various racial and ethnic groups equally, and is therefore not fully generalizable to the general population. The precise localization of the tumor inside the brain stem is one of the best-known risk factors, and this kind of information was not available. It should also be noted that, even after selective statistical adjustment, the possibility of unmeasured confounding and selection bias still exists. Nevertheless, our study was the first major clinical study evaluating the complete spectra of age and histological tumor subtypes, and is therefore still clinically relevant with meaningful implications for clinical practice.

The results of the present study showed that older age (≥ 60 years) was a negative independent prognostic factor for OS and CSS in BG. Studies from Guillemo et al. and Landolfi et al. have reported a higher prevalence of high-grade gliomas in older than in younger patients (11,20), and statistical analysis reveals worse clinical outcomes for BG patients above 40 years of age (22). This may be explained by reduced biological function at older age, meaning reduced ability to tolerate ra-

Table I: Distribution of Demographics, Tumor, and Treatment Characteristics of Brainstem Glioma Patient from the SEER.

Variables	Overall N=1,660	Training set N=1,162	Validation set N=498	p-value
	n (%)	n (%)	n (%)	
Age (years)				0.332
< 20	905 (55)	616 (53)	289 (58)	
20-59	565 (34)	403 (35)	162 (33)	
≥ 60	190 (11)	143 (12)	47 (9.4)	
Size (mm)				0.724
< 20	347 (21)	249 (21)	98 (20)	
≥ 20	1,313 (79)	913 (79)	400 (80)	
Sex				0.748
Female	793 (48)	548 (47)	245 (49)	
Male	867 (52)	614 (53)	253 (51)	
Race				0.835
Black	179 (11)	120 (10)	59 (12)	
White	1,346 (81)	951 (82)	395 (79)	
Others	135 (8.1)	91 (7.8)	44 (8.8)	
Marriage				0.178
Married	413 (25)	309 (27)	104 (21)	
Single	1,149 (69)	788 (68)	361 (72)	
DSW	98 (5.9)	65 (5.6)	33 (6.6)	
Surgery				0.870
Total gross resection	240 (14)	170 (15)	70 (14)	
Partial resection	279 (17)	188 (16)	91 (18)	
Biopsy	153 (9.2)	114 (9.8)	39 (7.8)	
No surgery	988 (60)	690 (59)	298 (60)	
Histological Type				0.905
Ependymoma	288 (17)	208 (18)	80 (16)	
Oligodendroglial tumors	18 (1.1)	13 (1.1)	5 (1.0)	
Non-glioblastoma astrocytoma	492 (30)	334 (29)	158 (32)	
Glioma, NOS	719 (43)	500 (43)	219 (44)	
Glioblastoma	143 (8.6)	107 (9.2)	36 (7.2)	
Radiation				0.128
No/Unknown	678 (41)	456 (39)	222 (45)	
Yes	982 (59)	706 (61)	276 (55)	
Chemotherapy				0.832
No/Unknown	1,025 (62)	712 (61)	313 (63)	
Yes	635 (38)	450 (39)	185 (37)	

DSW: Divorced & separated & widowed

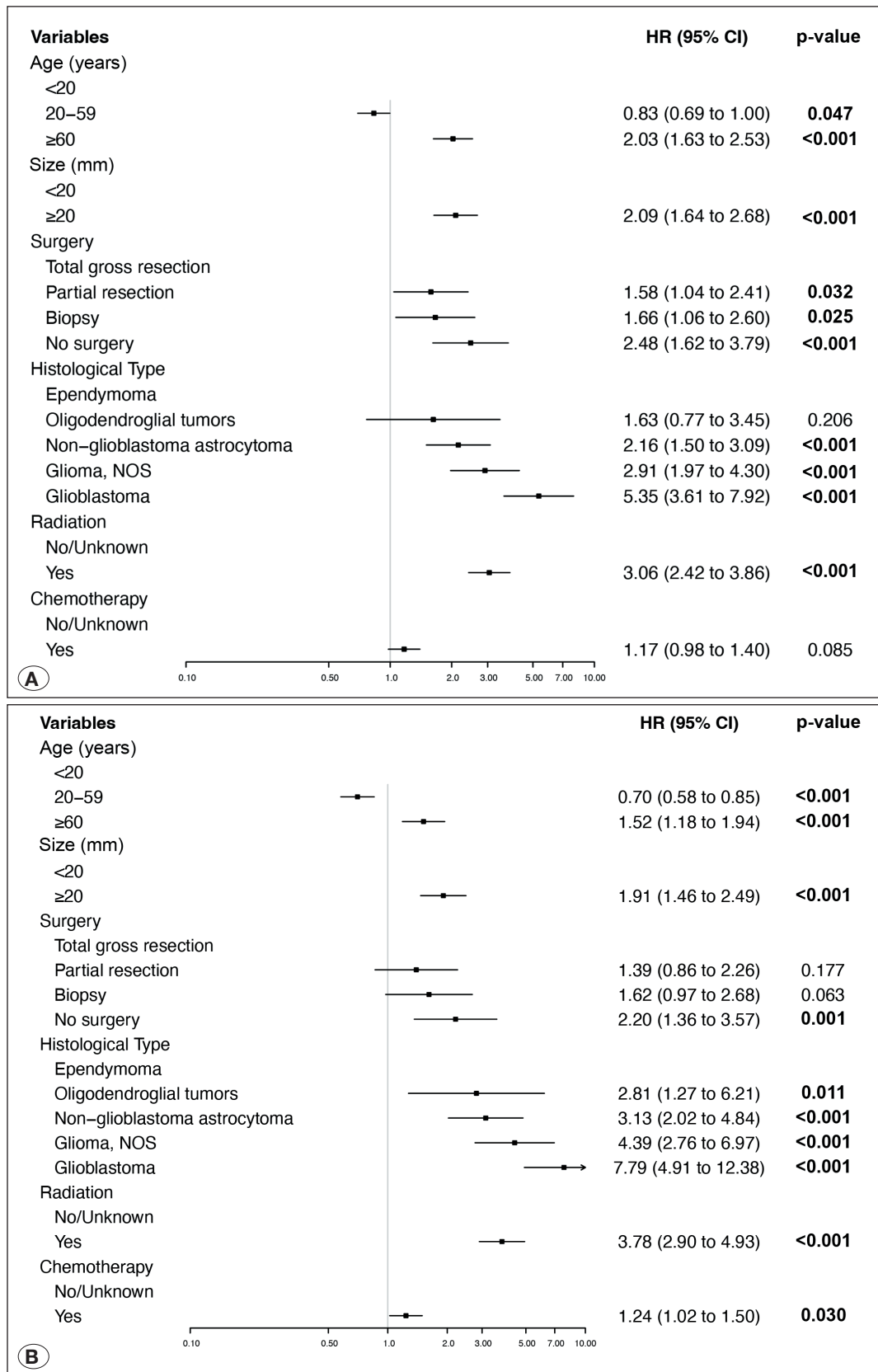


Figure 2: Forest plots and multivariate Cox regression analysis of factors associated with overall survival **(A)** and cancer-specific survival **(B)** of brainstem glioma.

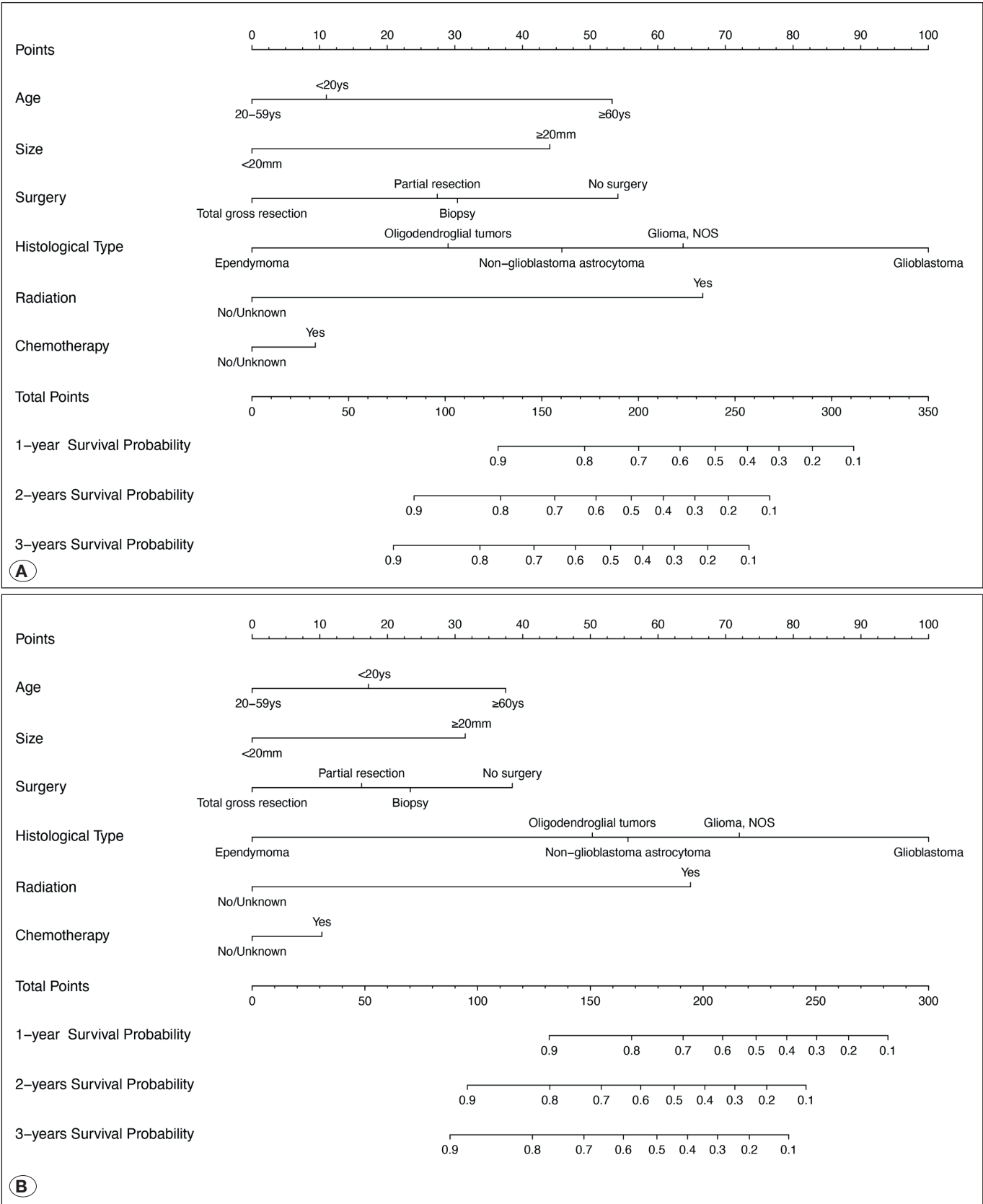


Figure 3: Nomograms for brainstem glioma to predict overall survival (A) and cancer-specific survival (B).

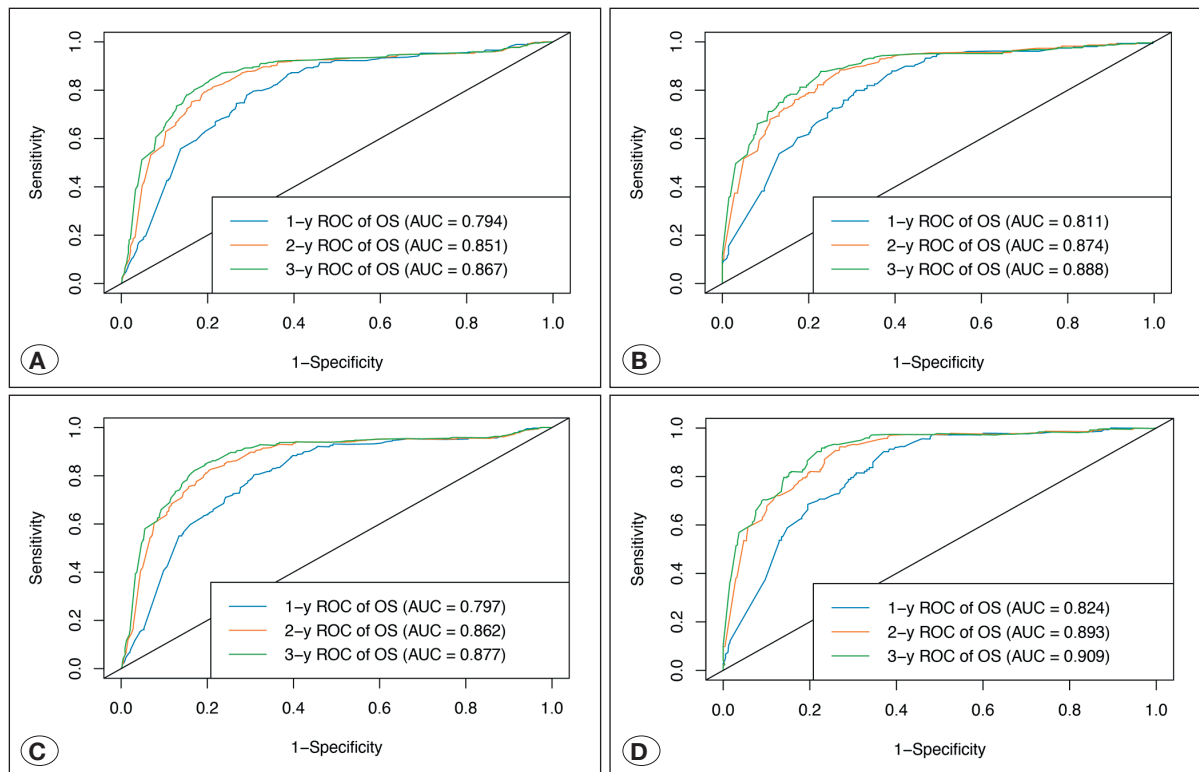


Figure 4: Receiver operating characteristic (ROC) curves and the area under the curve (AUC) of nomograms at 1-, 2-, and 3- years for overall survival—the training (A) and testing (B) set, and cancer-specific survival—the training (C) and testing (D) set.

diotherapy and chemotherapy (37). This even extends to the treatment of focal brainstem tumors, with the incidence of operations in older patients being less than in younger groups. This may be explained by the calculated risk related to surgical complications and anesthesia. Overall, high-grade gliomas are less prevalent in adults from 20 to 59 years of age. Younger adult patients may be in better physical condition, and therefore have the potential to tolerate intensive treatment better. Adult patients, in general, are expected to better withstand toxicities related to radiation injury and systemic chemotherapies. Our results also suggest that an age between 20 and 59 years is an independent, favorable prognostic factor in BG.

High-grade gliomas are more malignant and have a higher propensity to disseminate along white matter tracts. Diffuse BGs have been observed to be more prone to involve the entire brainstem (41). Conversely, increased tumor size often signifies a more malignant nature, imposing more substantial challenges for treatment. Furthermore, malignant BGs exhibit a higher degree of resistance to chemotherapy and radiotherapy (36). Even with cytoreductive surgery, recurrence is often rapid. The present study corroborates these observations, confirming that both tumor size and histological type are critical, independent prognostic factors for BG.

The precise location of surgery in the management of BG remains inadequately discussed. Before the development of magnetic resonance imaging, operating on brainstem tumors carried severe risk of mortality and complications, and was

absolutely contraindicated. With developments in imaging, intraoperative monitoring, and knowledge of safe entry regions and neuronavigation, brainstem surgery is no longer considered life-threatening, and is becoming more accepted (15). A large body of work has established that surgical resection for focal BGs results in enhanced patient outcomes (7,9,14,29). Our results also indicate a positive correlation of GTR with OS and CSS. For low-grade BGs, 68% of patients with focal tumors achieve GTR (14). There are now various safe and effective surgical resection techniques available, depending on tumor location. Safe entry zones and intraoperative monitoring have optimized maximal surgical resection while reducing the occurrence of surgical complications and mortality (14). Cytoreductive surgery in cases for which GTR is not feasible has proved beneficial for low-grade glioma (34). Even for diffuse BGs, partial resection results in significantly better survival rates than those of patients who do not undergo surgery (9). Thus, individualized therapeutic planning, considering age, tumor dimension, histology, and tumor site, is required for the indication of the surgical treatment.

Radiotherapy remains the dominant treatment for BG (46). Radiotherapy has a meaningful benefit in terms of progression-free survival for low-grade BGs (34). The HR for radiotherapy is not statistically significant for high-grade BGs (12,46). Radiotherapy exhibits delayed adverse effects, such as neurocognitive toxicity, secondary neoplastic effects, and cerebrovascular accidents (3,8). Meanwhile, the efficacy of chemotherapy drug treatments for BG has so far failed to meet early

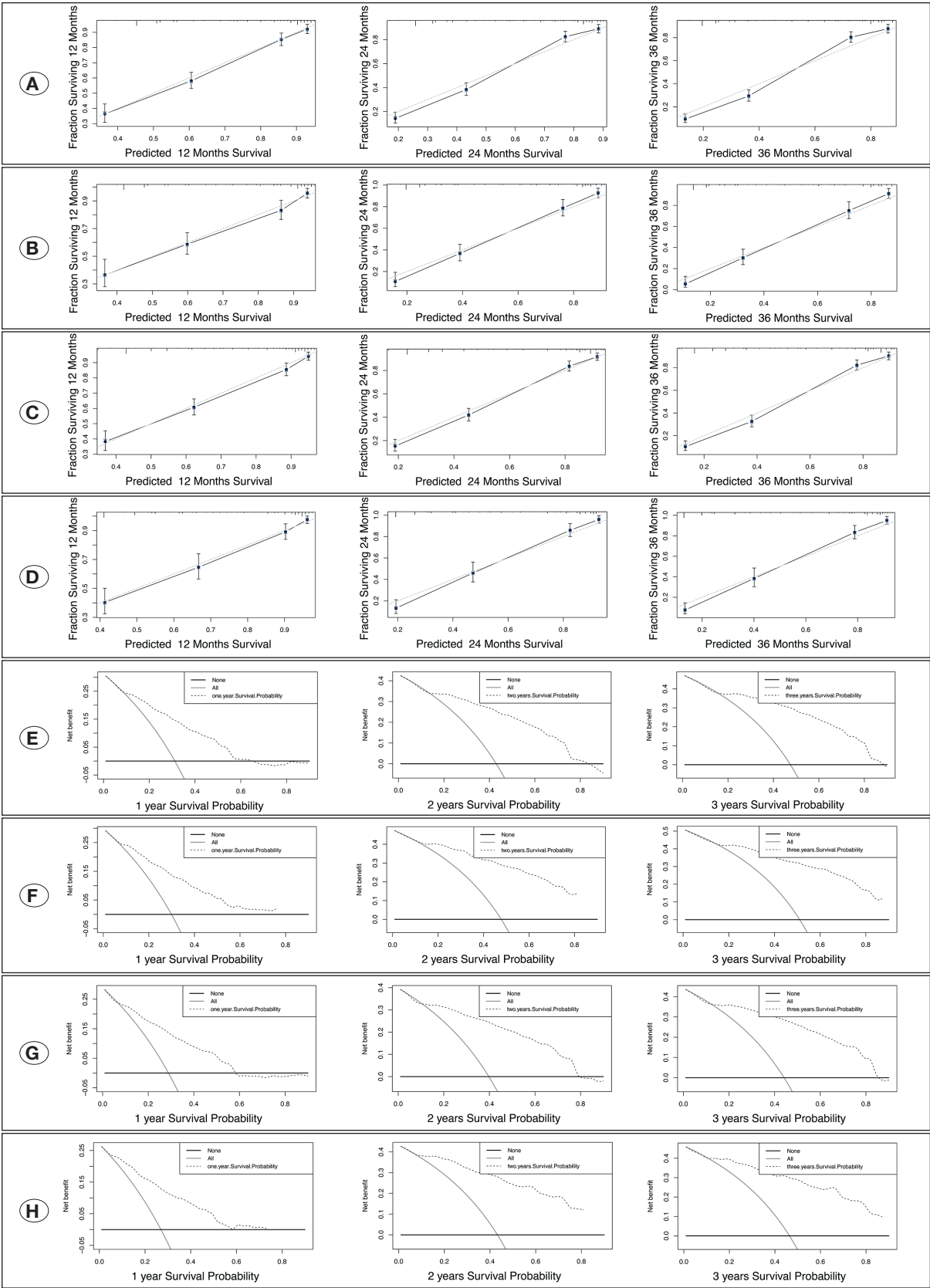


Figure 5: The calibration curve of the prognostic nomogram for overall survival—the training (A) and testing (B) set, and cancer-specific survival—the training (C) and testing (D) set. The decision curve analysis (DCA) of the prognostic nomogram for overall survival—the training (E) and testing (F) set, and cancer-specific survival—the training (G) and testing (H) set.

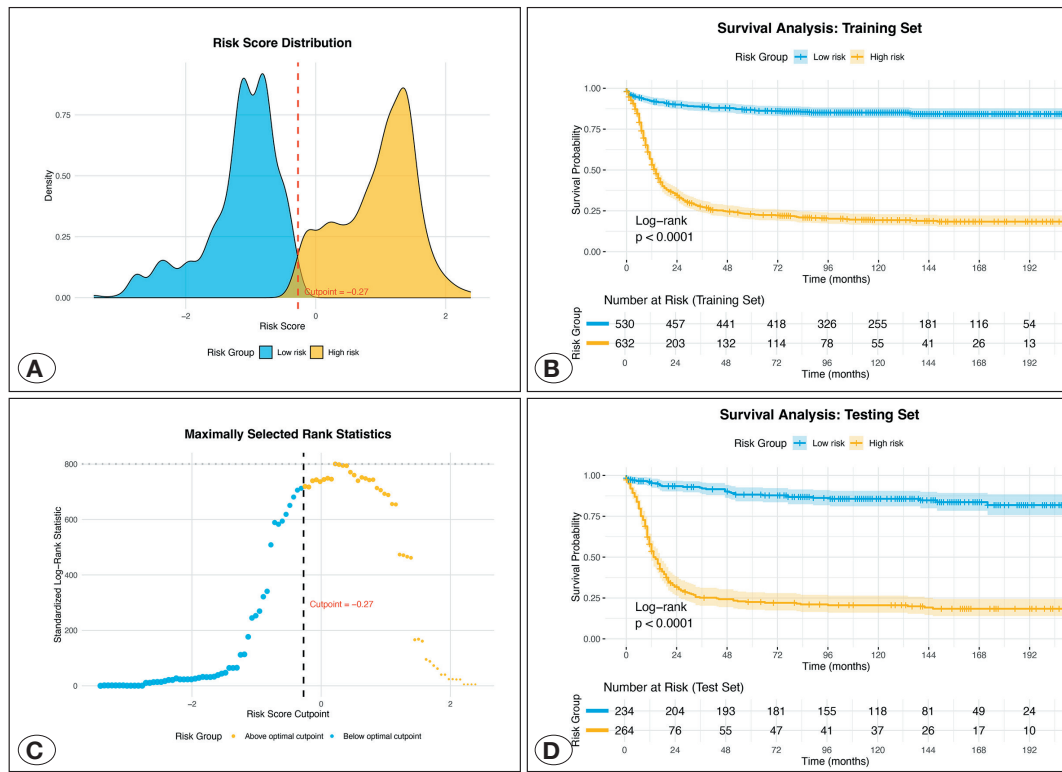


Figure 6: On the basis of the optimum cutoff value (-0.27) (A,B), patients were categorized into low-risk and high-risk groups for cancer-specific survival. The Kaplan-Meier survival curve of these two groups: The training (C) and the testing (D) set.

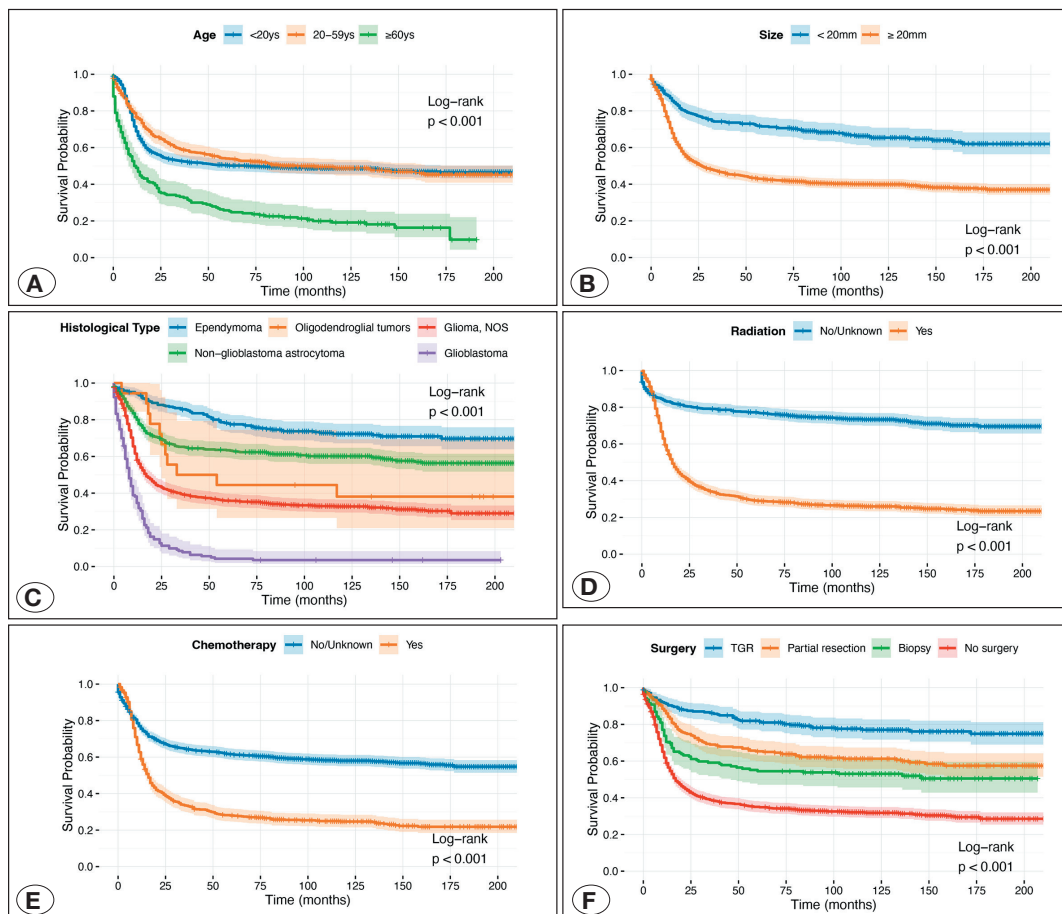


Figure 7: Kaplan-Meier survival curves based on the independent prognostic factors of overall survival.

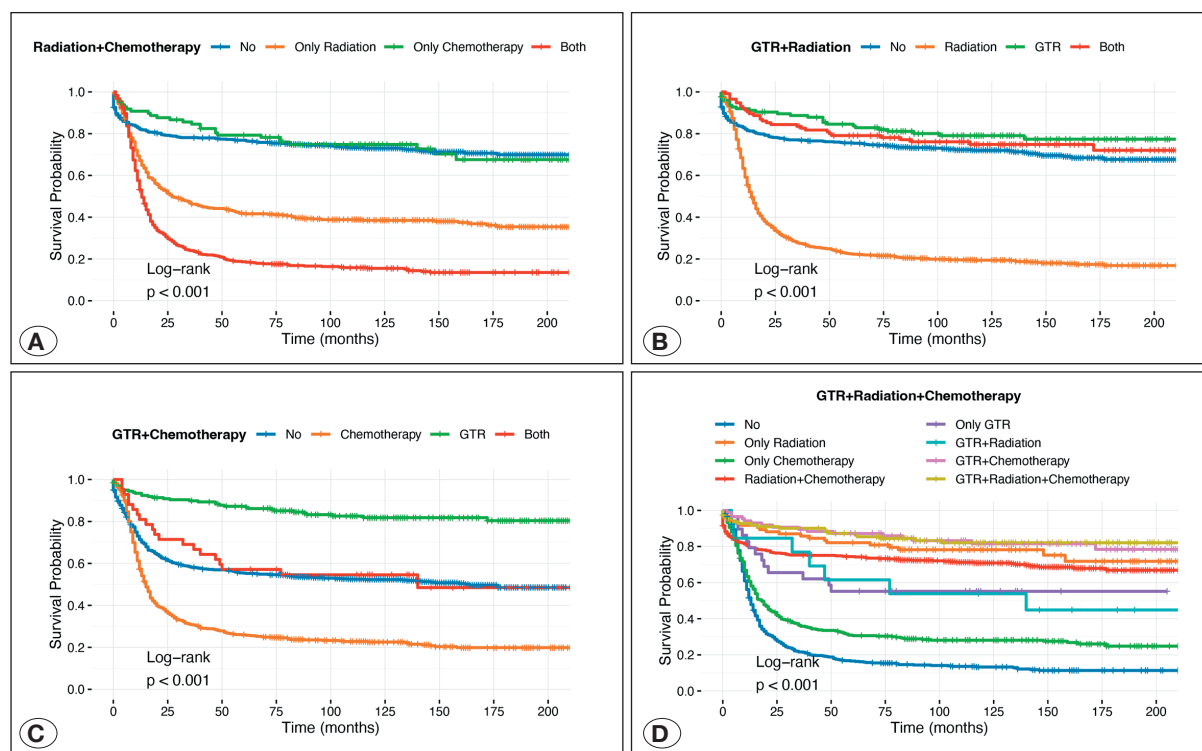


Figure 8: Kaplan–Meier survival curves based on the treatment methods stratification of overall survival.

optimism. Many research papers—including patient series involving different glioma grades—have difficulty accurately separating out the effects of chemotherapy drugs (36). A lack of unified clinical guidelines has also resulted in the adoption of different and uneven chemotherapy regimens for BG (14). This may explain the differing clinical follow-up outcomes for patients with radiotherapy and/or chemotherapy in our study.

Research on BG is evolving rapidly. The detection of H3K27 and IDH mutations in circulating tumor DNA from cerebrospinal fluid holds significant potential (23). Magnetic resonance spectroscopy can be used to assess the extent of H3K27 alteration (6) and evaluate the malignancy grade of brainstem tumors (40). Recent clinical trials have demonstrated the preliminary efficacy of novel therapeutic approaches, including oncolytic viruses (33) and CAR-T cell therapy (30,42).

Simultaneously, imaging modalities are increasingly being used to visualize brainstem tumors (10,31,47), playing a crucial role in determining the extent of lesions and assisting surgery. Due to the blood-brain barrier, traditional chemotherapeutic drugs cannot reach intracranial lesions. However, numerous studies have reported on improving drug delivery methods, such as the use of nanomaterials, liposomes, and exosomes (5,18,19,48). These small molecules can cross the blood-brain barrier and utilize the acidic conditions of the tumor microenvironment to target tumor tissue. This will undoubtedly advance the treatment of BG. The use of various methods for tumor reduction, including chemotherapy, can also increase a patient's probability of surgical eligibility at a later stage. Even for patients who are not candidates for surgery, this approach can prolong survival.

CONCLUSION

Overall, this large-scale, SEER database-based study identified age, tumor size, histologic type, surgery, radiotherapy, and chemotherapy as independent prognostic factors for OS and CSS in BG. The effectiveness and influence of surgical treatment, radiotherapy, and chemotherapy for BG were synthesized and confirmed, and the significance of surgical operation in some of these cases was reaffirmed. Moreover, we constructed and validated prognostic nomograms for one-, two-, and three-year OS and CSS for BG.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, not-for-profit, or commercial sectors.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Disclosure: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: XW, CX

Data collection: CX

Analysis and interpretation of results: CX, YZ

Draft manuscript preparation: CX, YZ

Critical revision of the article: XW, ZL

Other (study supervision, fundings, materials, etc.): XW, ZL

All authors (CX, YZ, XW, ZL) reviewed the results and approved the final version of the manuscript.

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